REMARKS

I. The invention

The present invention relates to a tissue adhesive comprising fibrinogen and an elastase inhibitor, wherein the elastase inhibitor is capable of inhibiting fibrinolysis.

II. Status of the claims

Claims 29, 30, 33, 36-42, 51, 54-60, and 70-73 are under examination. Claims 31, 32, 34, 35, 43-50, 52, 53, and 61-69 are withdrawn from consideration.

III. Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 29, 30, 33, 36-42, 51, 54-60, and 70-73 under 35 USC §103(a) as allegedly being obvious over U.S. Patent No. 5,418,221 (Hammarstrom) or U.S. Patent No. 5,631,011 (Wadstrom) in view of U.S. Patent No. 5,271,939 (Robertson) or WO 92/22309 (Mehta) and further in view of U.S. Patent No. (Akinson). Applicants respectfully traverse this rejection.

Evidence of secondary considerations such as unexpected results can be used to overcome a *prima facie* case of obviousness and establish the non-obviousness of a claimed invention. See *In re Soni*, 34 USPQ2d 1684 (Fed. Cir. 1995). The Examiner states that one of skill in the art would have been motivated to combine the elements of the present invention, a fibrinogen adhesive and an elastase inhibitor, as each of these components are generally used in wound healing. However, even if one of skill in the art would have been motivated to combine the elements of the present invention, the unexpected result of fibrinolysis-inhibition arising from the use of an elastase inhibitor with a fibrinogen-based tissue adhesive is sufficient to overcome a *prima facie* case of obviousness.

The claims recite a tissue adhesive comprising fibrinogen and an elastase inhibitor. Each of these elements (fibrinogen and elastase inhibitors) are separately disclosed in the cited art as generally used in wound healing. With respect to the

fibrinogen-based tissue adhesives, Waldstrom discloses the use of such compositions generally for wound healing and other therapeutic uses, while Hammarstrom focuses on the use of such compositions for wound healing in dental surgeries.

With respect to elastase inhibitors, Robertson discloses the use of elastase inhibitors for treatment and prevention of corneal scar formation during laser surgery. These elastase inhibitors were used as epithelial cell health promoters known to contribute to the overall health of epithelial cells of the cornea (column 11 lines 37-44 and column 12 lines 3-15). Mehta discloses the use of the elastase inhibitor, 4-(4-chlorophenyl-sulphonylcarbamoyl)benzoyl-L-valyl-L-proline 1(RS)-(1-trifluoroacetyl-2-methylpropyl)amide, for treating vascular disease. This compound is used to inhibit neutrophil infiltration and subsequent tissue injury. Atkinson discloses the use of an elastase inhibitor, eglin, in toothpaste, mouthwash, and skin cream compositions for cosmetic and therapeutic purposes.

For fibrinogen-based tissue adhesives, it is desirable to control the durability of the sealant by inhibiting fibrinolysis. Plasmin-mediated fibrinolysis is known, and plasmin inhibitors have been previously used to prevent premature fibrinolysis of a fibrinogen-based tissue adhesive. However, the present invention demonstrates that elastase inhibitors are surprisingly effective in preventing premature fibrinolysis of fibrinogen-based tissue adhesives via a non-plasmin fibrinolytic pathway.

Example I shows an *in vitro* test for assaying the fibrinolysis-inhibiting action of the elastase inhibitors of the invention. Elastase inhibitors eglin and α1-anti-protease were admixed with a fibrinogen-based tissue adhesive. The ability of these elastase inhibitors to prevent fibrinolysis of the tissue adhesive was compared to that of aprotinin, a plasmin inhibitor. Surprisingly, figures 1 and 2 show that the elastase inhibitors were at least as effective, if not more effective, than the plasmin inhibitor in prevention fibrinolysis of the fibrinogen-based tissue adhesive, as compared to the fibrinogen-based tissue adhesive alone.

all Graphs show same results without moist both ingredients.

Example II shows *in vivo* tests using both hyper-fibrinolytic and normal - fibrinolytic conditions. Fibrinogen-based tissue adhesives containing eglin, an elastase inhibitor, were compared to tissue adhesives alone or those containing aprotinin, a plasmin inhibitor. Surprisingly, figures 3 and 4 show that the elastase inhibitors were at least as effective, if not more effective, than the plasmin inhibitor in prevention fibrinolysis of the fibrinogen-based tissue adhesive, as compared to the fibrinogen-based tissue adhesive alone.

All goals at same level. no difference levels with or without both ingredients

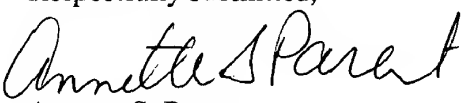
Thus, the present invention demonstrates that elastase inhibitors, when used in combination with a fibrinogen-based tissue adhesive, have the unexpected property of preventing fibrinolysis of the adhesive. These elastase inhibitors can be used alone or in combination with plasmin inhibitors to prevent premature fibrinolysis of a fibrinogen-based tissue adhesive. Applicants respectfully submit that any *prima facie* case of obviousness has been properly rebutted by submission of secondary evidence of unexpected results, and thus request the withdrawal of the rejections under 35 USC §103.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (415) 576-0200.

Respectfully submitted,



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